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# Associations of demographic and clinical factors with depression over 2.5-years in an international prospective cohort of people living with MS

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ABSTRACT

*Background:* Depression is highly prevalent among people with MS, and determinants thereof would be useful.
*Objectives:* We examined the relationship of demographic and clinical factors with positive depression-screen and change in depression over 2.5 years in people with MS.
*Methods:* Positive depression-screen assessed by Patient Health Questionnaire (PHQ)-2 and PHQ-9. Associations of demographic and clinical factors with depression-screen and change thereof assessed using multivariable regression models, adjusted for age, sex, disability, fatigue, antidepressant use, and baseline PHQ-2, as appropriate.
*Results:* Overweight/obese BMI, comorbidity number, fatigue, and disability were associated with positive depression-screen, while married/partnered state, being employed, higher perceived socioeconomic status, and greater education were inversely associated with depression-screen. After adjustment, only marital status, socioeconomic status, antidepressant medication use, and fatigue were associated with risk of newly positive depression-screen. MS type, relapse number and immunomodulatory medication use were not associated with depression-screen after controlling for disability and fatigue.
*Conclusion:* In a large prospective cohort study of depression in people with MS, we substantiated several potential determinants of a positive depression-screen and depression trajectory, particularly fatigue. Given that fatigue is the most common and most significant clinical symptom for people with MS, efforts to reduce fatigue may have follow-on benefits for reducing depression.

## 1. Introduction

Depression is common among people with MS, with estimates ranging from 20–50% in various studies (Koch et al., 2008; Patten et al., 2017; Wood et al., 2012; Zigmond and Snaith, 1983). Understanding the characteristics of depression in people living with MS, and particularly what drives the onset and recovery from depression, is important in improving their quality of life.

We have previously described the characteristics of screening positive for depression in this sample at baseline ($n$ = 2459)(Taylor et al., 2014), finding 19.3% screened positive for depression as measured by the Patient Health Questionnaire (PHQ)-2(Lowe et al., 2005), and that positive depression-screen was more common among participants with higher BMI and those with greater fatigue and disability, but less common among those who were partnered, employed or more educated. These results are similar to those found in an Australian study of participants with established MS ($n$ = 198) using the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983), which found a positive depression-screen frequency of 18.5% and that positive depression-screen was more prevalent among those with greater disability and fatigue (Wood et al., 2012). Similar frequencies of depression have been found early after symptom onset: in an Australian multicentre cohort of people recruited soon after symptom onset ($n$ = 236), the frequency of positive depression-screen as measured by HADS was 16.0% (Simpson et al., 2016), greater disability associated with positive depression-screen. Studies of depression in MS using other depression screening tools have found similar results (Brown et al., 2009; Chwastiak et al., 2002; Solaro et al., 2016), with fatigue the most consistent determinant.

Several longitudinal studies have been undertaken, examining change in depression over time. Wood and colleagues ($n$ = 198) found

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the frequency of positive depression-screen increased by 7.3% per year of follow-up over 2.3 years, strongly predicted by disability (Wood et al., 2012). The BEYOND clinical trial ($n$ = 891 with depression data) examined depression using the Beck Depression Inventory-II, finding an average frequency of positive depression-screen of 25–30%, not greatly varying over three years of follow-up (Schippling et al., 2016). Koch and colleagues followed a subgroup of 94/228 patients with baseline depression data for ten years, finding the proportion with clinically significant depression as measured by the Center for Epidemiologic Studies Depression Scale increased from 47.9% to 52.1% (Koch et al., 2008).

While there are many cross-sectional studies examining mood and depression in MS, there is a comparative lack of prospective studies of change in depression in large representative samples. We undertook a prospective cohort study among an international sample of people living with MS followed over 2.5 years, examining the demographic and clinical characteristics of positive depression-screen at 2.5-year review, and of change in depression-screen during follow-up. Of note, the lifestyle determinants of depression-screen during this same period are described in another article (Taylor et al., 2018).

## 2. Methods

### 2.1. Participants and data collection

Participants were enrolled in the HOLISM study for which methodology has been described previously (Hadgkiss et al., 2013; Weiland et al., 2018). Participants were recruited via online platforms, and SurveyMonkey® was used to provide respondents with a participant information sheet and survey. Inclusion criteria required participants be ≥18 and self-reporting a physician diagnosis of MS. The University of Melbourne Health Sciences Human Ethics Sub-Committee provided ethical approval; all participants provided informed consent.

A range of demographic, lifestyle, and clinical parameters were measured as described previously (Hadgkiss et al., 2013; Weiland et al., 2018). BMI was estimated from participant-reported height (metres) and weight (kilograms) using the function, weight/height$^2$. Perceived relative socioeconomic status (PRSES) was queried as a 9-unit Likert scale, ranging from Poorest to Richest. Disability was assessed using the Patient-Determined Disease Steps (PDDS) scale (Hohol et al., 1995), from which the disease-duration-adjusted Patient-derived Multiple Sclerosis Severity Score (P-MSSS) was calculated (Kister et al., 2013). Fatigue was assessed using the Fatigue Severity Scale (FSS) (Krupp et al., 1989). Doctor-diagnosed relapse number in the preceding year was also queried.

Depression risk was assessed using the PHQ, which has been validated in MS populations (Marrie et al., 2017), using the two-question instrument (PHQ-2) (Lowe et al., 2005) at baseline and the nine-question instrument (PHQ-9) at follow-up (Kroenke et al., 2001). As the PHQ-2 is nested within the PHQ-9, we could calculate the PHQ-2 score at follow-up as well. The PHQ-9 comprises nine questions; participants are asked to mark the frequency that they have experienced that symptom in the preceding two weeks, options including “Not at all”, “Several days”, “More than half the days”, and “Nearly every day”. Note the asterixed items are those included in the PHQ-2.

1) Little interest or pleasure in doing things*
2) Feeling down, depressed of hopeless*
3) Trouble falling asleep or staying asleep, or sleeping too much
4) Feeling tired or having little energy
5) Poor appetite or overeating
6) Feeling bad about yourself – or that you are a failure or having let yourself or your family down
7) Trouble concentrating on things, such as reading the newspaper or watching television
8) Moving or speaking so slowly that other people could have noticed; or the opposite, being so fidgety or restless that you have been moving around a lot more than usual
9) Thoughts that you would be better off dead or hurting yourself in some way.

PHQ responses were scored from 0–3, and these summated. The PHQ-2 scores ranged 0–6, >2 indicating positive depression-screen. The PHQ-9 scores ranged 0–27, >9 indicating positive depression-screen; the PHQ-9 is also subdivided: 5–9 indicating minimal depression symptoms, 10–14 mild-major depression, 15–19 moderate-major depression, and 20–27 severe-major depression. Given cell-size constraints ($n$ = 37 with severe-major depression), the latter two groups were combined into moderate/severe-major depression.

## 3. Statistical analysis

Agreement between PHQ-2 and PHQ-9, the latter used as the reference-standard, was assessed by unweighted kappa test (Cohen, 1960). In addition, sensitivity (true positive/total testing positive) and specificity (true negative/total testing negative) (International Epidemiological Association, 2001) were calculated.

Log-binomial regression models were used to evaluate factors associated with positive depression-screen at follow-up and log-multinomial regression models (Blizzard and Hosmer, 2007) used to evaluate factors associated with PHQ-9 severity, both estimating prevalence ratios. Multivariable models were adjusted for age, P-MSSS, fatigue, and antidepressant medication use, these covariates selected based on review of the literature for relevant characteristics.

Log-binomial regression were used to evaluate factors associated with change in PHQ-2-defined depression-screen during follow-up. In these analyses, those who changed from positive to negative depression-screen were compared to those who screened positive for depression at both timepoints, while those who changed from negative to positive depression-screen were compared to those who screened negative for depression at both timepoints. Multivariable models for predictors of change in depression-screen were adjusted for age, P-MSSS, fatigue, antidepressant medication use, and baseline continuous PHQ-2 score.

All multivariable models were done using complete-case analysis; that is, constrained to those who had data on all model covariates.

STATA/SE 15.0 (StataCorp, College Park, USA) was used for data analysis.

## 4. Results

At baseline, 2503 participants initiated the questionnaire, of whom 2224 (88.9%) completed the PHQ-2 instrument. At 2.5-year review, 1441 participants (57.6% retention rate) initiated the questionnaire, of whom 1264 (90.2%) completed the PHQ-9 instrument.

As described elsewhere (Hadgkiss et al., 2013; Weiland et al., 2018), the cohort was majority female at both timepoints, of mean age in the mid-40s and the mean BMI was in the overweight range. Roughly three-quarters of participants reported relapsing-remitting MS (RRMS), median duration from diagnosis of 6 years, and a low level of disability, though clinically significant fatigue was present in approximately two-thirds of participants at both timepoints. At baseline, immunomodulatory medication use was reported in 46.7%, decreasing to 42.0% at follow-up. Prescription antidepressant use was reported by roughly 17% of participants at baseline and follow-up. Other cohort characteristics are shown in Supplemental Table 1.

### 4.1. Prevalence & determinants of positive depression-screen

At 2.5-year review, the prevalence of PHQ-2 positive depression-screen was 14.5%, significantly decreased from that seen at baseline (19.1%, $p$ = 0.002). However, the prevalence of PHQ-9 positive depression- screen at 2.5-year review was higher (21.7%). The kappa statistic for inter-rater agreement was 62.4% ($p$ < 0.001), observed agreement significantly greater than expected by chance (88.8% vs 70.3%). The sensitivity and specificity of the PHQ-2 as compared to the PHQ-9 were 56.9% and 97.7%, respectively.

**Table 1**
Associations of demographic covariates with positive depression-screen at 2.5-year follow-up, as measured by PHQ-2 & PHQ-9.

| | *n/N* with PHQ-2 > 2 (%) | Univariable | Adjusted[a] | *N* with PHQ-9 > 9 (%) | Univariable | Adjusted[a] |
|---|---|---|---|---|---|---|
| Age | | | | | | |
| 18–38 | 32/232 (13.8%) | 1.00 [Reference] | 1.00 [Reference] | 47/226 (20.8%) | 1.00 [Reference] | 1.00 [Reference] |
| >38–46 | 43/319 (13.5%) | 0.98 (0.64, 1.50) | 0.82 (0.55, 1.23) | 64/310 (20.7%) | 0.99 (0.71, 1.39) | 0.82 (0.61, 1.12) |
| >46–54 | 59/343 (17.2%) | 1.25 (0.84, 1.86) | 0.83 (0.56, 1.22) | 81/332 (24.4%) | 1.17 (0.85, 1.61) | 0.78 (0.58, 1.05) |
| >54–87 | 56/415 (13.5%) | 0.98 (0.65, 1.47) | **0.67 (0.45, 1.00)** | 82/396 (20.7%) | 1.00 (0.72, 1.37) | **0.65 (0.48, 0.88)** |
| *Trend:* | | *p = 0.86* | *p = 0.055* | | *p = 0.83* | ***p = 0.005*** |
| Marital status | | | | | | |
| Not married/partnered | 59/305 (19.3%) | 1.00 [Reference] | 1.00 [Reference] | 80/293 (27.3%) | 1.00 [Reference] | 1.00 [Reference] |
| Married/partnered | 128/992 (12.9%) | **0.67 (0.50, 0.88)** | **0.71 (0.54, 0.93)** | 190/960 (19.8%) | **0.73 (0.58, 0.91)** | **0.79 (0.64, 0.98)** |
| | | ***p = 0.005*** | ***p = 0.014*** | | ***p = 0.005*** | ***p = 0.033*** |
| Number of people in support network | | | | | | |
| 0 | 13/43 (30.2%) | 1.00 [Reference] | 1.00 [Reference] | 18/40 (45.0%) | 1.00 [Reference] | 1.00 [Reference] |
| 1 | 56/269 (20.8%) | 0.69 (0.41, 1.15) | 0.84 (0.53, 1.31) | 81/260 (31.2%) | 0.69 (0.47, 1.02) | 0.82 (0.57, 1.18) |
| 2 – 5 | 95/784 (12.1%) | **0.40 (0.25, 0.66)** | **0.53 (0.35, 0.82)** | 141/758 (18.6%) | **0.41 (0.29, 0.60)** | **0.50 (0.36, 0.72)** |
| >5 | 12/155 (7.7%) | **0.26 (0.13, 0.52)** | **0.37 (0.19, 0.73)** | 18/151 (11.9%) | **0.27 (0.15, 0.46)** | **0.38 (0.22, 0.64)** |
| *Trend:* | | ***p < 0.001*** | ***p < 0.001*** | | ***p < 0.001*** | ***p < 0.001*** |
| Employment status | | | | | | |
| Not employed | 106/595 (17.8%) | 1.00 [Reference] | 1.00 [Reference] | 163/568 (28.7%) | 1.00 [Reference] | 1.00 [Reference] |
| Employed | 84/706 (11.9%) | **0.67 (0.51, 0.87)** | 1.01 (0.77, 1.33) | 111/688 (16.1%) | **0.56 (0.45, 0.70)** | **0.78 (0.64, 0.98)** |
| | | ***p = 0.003*** | *p = 0.96* | | ***p < 0.001*** | ***p = 0.036*** |
| Level of education completed | | | | | | |
| None/primary/secondary | 51/257 (19.8%) | 1.00 [Reference] | 1.00 [Reference] | 76/249 (30.5%) | 1.00 [Reference] | 1.00 [Reference] |
| Vocational school | 35/197 (17.8%) | 0.90 (0.61, 1.32) | 0.95 (0.65, 1.39) | 49/191 (25.7%) | 0.84 (0.62, 1.14) | 0.88 (0.66, 1.18) |
| Bachelor's degree | 70/492 (14.2%) | **0.72 (0.52, 1.00)** | 0.93 (0.68, 1.28) | 92/472 (19.5%) | **0.64 (0.49, 0.83)** | 0.80 (0.62, 1.03) |
| Post-graduate study | 33/358 (9.2%) | **0.47 (0.31, 0.70)** | **0.65 (0.44, 0.96)** | 55/347 (15.9%) | **0.52 (0.38, 0.71)** | **0.67 (0.50, 0.89)** |
| *Trend:* | | ***p < 0.001*** | ***p = 0.038*** | | ***p < 0.001*** | ***p = 0.004*** |
| Perceived socioeconomic status relative to peers | | | | | | |
| Lower | 66/255 (25.9%) | **1.64 (1.21, 2.22)** | 1.20 (0.89, 1.62) | 101/247 (40.9%) | **1.93 (1.51, 2.46)** | **1.50 (1.18, 1.90)** |
| Same | 65/411 (15.8%) | 1.00 [Reference] | 1.00 [Reference] | 83/391 (21.2%) | 1.00 [Reference] | 1.00 [Reference] |
| Higher | 59/636 (9.3%) | **0.59 (0.42, 0.82)** | 0.73 (0.53, 1.01) | 88/619 (14.2%) | **0.67 (0.51, 0.88)** | 0.83 (0.64, 1.08) |
| *Trend:* | | ***p < 0.001*** | ***p = 0.002*** | | ***p < 0.001*** | ***p < 0.001*** |

Analyses by log-binomial regression, estimating a prevalence ratio (PR) (95% CI).
Figures in boldface denote statistical significance ($p < 0.05$). Figures in italics are *p*-values.
Abbreviations: FSS = Fatigue Severity Scale; PHQ = Patient Health Questionnaire; P-MSSS = Patient Determined Multiple Sclerosis Severity Score.
[a] Adjusted models adjusted for age, P-MSSS, FSS, and use of prescription antidepressant medication.

As in Table 1, being married/partnered was associated with significantly lower frequency of PHQ-2 and PHQ-9 positive depression-screen, persisting on adjustment. Analogous results were seen for social network number, a larger network associated with significantly smaller proportions with depression. Being employed and having completed more education were associated with lower frequencies of positive depression-screen, and PRSES was inversely associated with depression, though adjustment attenuated all these associations. Neither age or sex was significantly associated with positive depression-screen, though older age was inversely associated after adjustment.

Being overweight/obese at follow-up and greater comorbidity number were associated with a higher frequency of positive depression-screen, persisting on adjustment (Table 3). Antidepressant and anxiolytic medication use were associated with positive depression-screen, but the latter association was markedly reduced on adjustment for antidepressant use.

Compared to relapsing-remitting cases, the frequency of positive depression-screen was significantly higher among progressive cases, though these associations attenuated on adjustment for disability and fatigue. Greater relapse number in the preceding year was positively associated with depression-screen by both instruments, though only the PHQ-9 association persisted on adjustment. Disability and fatigue were both strongly positively associated with depression-screen by both scales, each largely resilient to mutual adjustment. Immunomodulatory medication use was not significantly associated with positive depression-screen, though use of interferon-β medication was positively associated with depression, reaching significance for PHQ-9.

### 4.2. Determinants of PHQ-9 depression severity

The inverse association seen between age and positive depression-screen was only evident for major depression (Table 3). The protective association of being married/partnered was solely evident for moderate/severe-major depression, whereas the benefits of a larger social network were seen for all grades of major depression. Employment was associated with all grades of depression, whereas the inverse association of education was only significant for moderate/severe-major depression. The positive association of PRSES was solely evident for major depression, while the inverse association of PRSES was present at all levels of depression.

The association of overweight/obese BMI with positive depression-screen was most evident for major depression (Table 4). Greater comorbidity number and antidepressant medication use were significantly associated with all grades of depression symptoms but was of greatest magnitude for major depression.

MS type was not significantly associated with depression grade. Greater disability was associated with major depression, albeit with mixed dose-dependency. Fatigue, however, showed pronounced dose-dependency, with 31.7-times greater frequency of moderate/severe-major depression among those with fatigue. Disease duration, while not significantly associated with PHQ-9 depression overall, was strongly and significantly associated with moderate/major severe depression. Immunomodulatory medication use was not associated with depression symptoms, though interferon-β was associated with moderate/severe-major depression.

### 4.3. Determinants of change in PHQ-2 between reviews

As in Table 5, neither sex nor age were significantly associated with change in depression. Those who were married/partnered at baseline were significantly less likely to become depressed after adjustment, but there was no impact of marital status on recovery from depression. Those with a larger social support network at baseline were less likely

**Table 2**
Associations of clinical covariates with positive depression-screen at 2.5-year follow-up, as measured by PHQ-2 & PHQ-9.

| | *n/N* with PHQ-2 > 2(%) | Univariable | Adjusted[a] | *N* with PHQ-9 > 9(%) | Univariable | Adjusted[a] |
|---|---|---|---|---|---|---|
| BMI | | | | | | |
| Underweight/normal | 85/790 (10.8%) | 1.00 [Reference] | 1.00 [Reference] | 117/766 (15.3%) | 1.00 [Reference] | 1.00 [Reference] |
| Overweight/obese | 15/517 (20.3%) | **1.89 (1.45, 2.46)** | **1.31 (1.01, 1.70)** | 157/496 (31.7%) | **2.07 (1.68, 2.56)** | **1.56 (1.27, 1.92)** |
| | | ***p* < 0.001** | ***p* = 0.042** | | ***p* < 0.001** | ***p* < 0.001** |
| Number of comorbidities as defined by SCQ | | | | | | |
| 0 | 48/631 (7.6%) | 1.00 [Reference] | 1.00 [Reference] | 68/618 (11.0%) | 1.00 [Reference] | 1.00 [Reference] |
| 1 | 50/361 (13.9%) | **1.82 (1.25, 2.65)** | 1.46 (1.00, 2.14) | 79/344 (23.0%) | **2.09 (1.55, 2.81)** | **1.74 (1.30, 2.34)** |
| 2 | 40/181 (22.1% | **2.91 (1.98, 4.27)** | **1.89 (1.26, 2.83)** | 57/174 (32.8%) | **2.98 (2.19, 4.06)** | **2.11 (1.53, 2.90)** |
| ≥3 | 52/136 (38.2%) | **5.03 (3.56, 7.10)** | **3.02 (2.06, 4.44)** | 70/128 (54.7%) | **4.97 (3.78, 6.54)** | **3.09 (2.28, 4.19)** |
| *Trend:* | | ***p* < 0.001** | ***p* < 0.001** | | ***p* < 0.001** | ***p* < 0.001** |
| Taking prescription antidepressant medication? | | | | | | |
| No | 114/1060 (10.8%) | 1.00 [Reference] | 1.00 [Reference] | 167/1031 (16.2%) | 1.00 [Reference] | 1.00 [Reference] |
| Yes | 76/249 (30.5%) | **2.84 (2.20, 3.66)** | **2.11 (1.63, 2.73)** | 107/233 (45.9%) | **2.84 (2.33, 3.45)** | **2.21 (1.81, 2.69)** |
| | | ***p* < 0.001** | ***p* < 0.001** | | ***p* < 0.001** | ***p* < 0.001** |
| Taking prescription anxiolytic medication? | | | | | | |
| No | 156/1,1904 (13.1%) | 1.00 [Reference] | 1.00 [Reference] | 226/1157 (19.5%) | 1.00 [Reference] | 1.00 [Reference] |
| Yes | 34/115 (29.6%) | **2.26 (1.65, 3.11)** | 1.28 (0.93, 1.77) | 48/107 (44.9%) | **2.30 (1.81, 2.92)** | **1.32 (1.03, 1.69)** |
| | | ***p* < 0.001** | *p = 0.13* | | ***p* < 0.001** | ***p* = 0.030** |
| Type of MS at completion of survey | | | | | | |
| Benign/RRMS | 102/853 (12.0%) | 1.00 [Reference] | 1.00 [Reference] | 157/826 (19.0%) | 1.00 [Reference] | 1.00 [Reference] |
| PPMS | 40/13 (20.7%) | **1.73 (1.25, 2.41)** | 1.23 (0.85, 1.76) | 45/186 (24.2%) | 1.27 (0.95, 1.70) | 0.88 (0.64, 1.19) |
| SPMS | 22/105 (21.0%) | **1.75 (1.16, 2.65)** | 1.32 (0.84, 2.07) | 32/102 (31.4%) | **1.65 (1.20, 2.27)** | 1.23 (0.86, 1.76) |
| PRMS | 3/22 (13.6%) | 1.14 (0.39, 3.32) | 0.67 (0.23, 1.98) | 8/22 36.4%) | **1.91 (1.08, 3.39)** | 1.16 (0.64, 2.08) |
| Unsure/other | 23/132 (17.4%) | 1.46 (0.96, 2.20) | 1.31 (0.88, 1.95) | 31/125 (24.8%) | 1.31 (0.93, 1.83) | 1.15 (0.83, 1.60) |
| Number of doctor-diagnosed relapses in preceding 12 months | | | | | | |
| 0 | 132/985 (13.4%) | 1.00 [Reference] | 1.00 [Reference] | 179/960 (18.7%) | 1.00 [Reference] | 1.00 [Reference] |
| 1 | 37/214 (17.3%) | 1.29 (0.92, 1.80) | 0.89 (0.63, 1.26) | 60/203 (29.6%) | **1.59 (1.23, 2.04)** | 1.20 (0.94, 1.53) |
| 2 | 7/44 (15.9%) | 1.19 (0.59, 2.39) | 0.61 (0.31, 1.22) | 13/40 (32.5%) | **1.74 (1.09, 2.78)** | 1.13 (0.73, 1.75) |
| ≥3 | 9/24 (37.5%) | **2.80 (1.63, 4.81)** | 1.18 (0.68, 2.05) | 13/22 (59.1%) | **3.17 (2.18, 4.60)** | **1.61 (1.08, 2.39)** |
| *Trend:* | | ***p* = 0.002** | *p = 0.58* | | ***p* < 0.001** | ***p* = 0.023** |
| P-MSSS disability | | | | | | |
| Mild disability (0–3) | 25/398 (6.3%) | 1.00 [Reference] | 1.00 [Reference] | 46/385 (12.0%) | 1.00 [Reference] | 1.00 [Reference] |
| Moderate disability (4–6) | 58/390 (14.9%) | **2.37 (1.51, 3.71)** | **1.60 (1.02, 2.49)** | 73/378 (19.3%) | **1.62 (1.15, 2.27)** | 1.12 (0.81, 1.54) |
| Severe disability (>6) | 104/506 (20.6%) | **3.27 (2.16, 4.96)** | **1.93 (1.26, 2.96)** | 147/487 (30.2%) | **2.53 (1.87, 3.42)** | **1.54 (1.15, 2.08)** |
| *Trend:* | | ***p* < 0.001** | ***p* = 0.002** | | ***p* < 0.001** | ***p* = 0.001** |
| Fatigue, as defined by FSS > 35 | | | | | | |
| No fatigue | 12/474 (2.5%) | 1.00 [Reference] | 1.00 [Reference] | 28/464 (6.0%) | 1.00 [Reference] | 1.00 [Reference] |
| Fatigue | 173/786 (22.0%) | **8.69 (4.90, 15.44)** | **6.37 (3.48, 11.65)** | 242/757 (32.0%) | **5.30 (3.65, 7.70)** | **4.20 (2.83, 6.24)** |
| | | ***p* < 0.001** | ***p* < 0.001** | | ***p* < 0.001** | ***p* < 0.001** |
| Disease duration from symptom onset, years | | | | | | |
| 2.91–8.19 | 38/327 (11.6%) | 1.00 [Reference] | 1.00 [Reference] | 50/318 (15.7%) | 1.00 [Reference] | 1.00 [Reference] |
| >8.19–14.23 | 47/324 (14.5%) | 1.25 (0.84, 1.86) | 1.16 (0.80, 1.69) | 66/312 (21.2%) | 1.35 (0.97, 1.88) | 1.23 (0.90, 1.67) |
| >14.23–23.20 | 52/328 (15.9%) | 1.36 (0.92, 2.01) | 1.13 (0.76, 1.67) | 75/319 (23.5%) | **1.50 (1.08, 2.06)** | 1.29 (0.93, 1.78) |
| >23.20–56.14 | 53/327 (16.2%) | 1.40 (0.95, 2.06) | 1.08 (0.71, 1.65) | 81/312 (26.0%) | **1.65 (1.20, 2.27)** | 1.30 (0.92, 1.84) |
| *Trend:* | | *p = 0.079* | *p = 0.75* | | ***p* = 0.001** | *p = 0.16* |
| Taking any of the 11 specified immunomodulatory[b] medications? | | | | | | |
| None | 103/723 (14.3%) | 1.00 [Reference] | 1.00 [Reference] | 138/698 (19.8%) | 1.00 [Reference] | 1.00 [Reference] |
| Interferon-β | 25/121 (20.7%) | 1.45 (0.98, 2.15) | 1.21 (0.83, 1.76) | 36/119 (30.3%) | **1.53 (1.12, 2.09)** | **1.34 (1.03, 1.75)** |
| Other | 62/465 (13.3%) | 0.94 (0.70, 1.25) | 0.75 (0.56, 1.00) | 100/447 (22.4%) | 1.13 (0.90, 1.42) | 0.91 (0.73, 1.14) |

Analyses by log-binomial regression, estimating a prevalence ratio (PR) (95% CI).
Figures in boldface denote statistical significance ($p < 0.05$). Figures in italics are *p*-values.
Abbreviations: BMI = Body mass index; FSS = Fatigue Severity Scale; PHQ = Patient Health Questionnaire; P-MSSS = Patient Determined Multiple Sclerosis Severity Score; PPMS = Primary progressive multiple sclerosis; PRMS = Progressive-relapsing multiple sclerosis; RRMS = Relapsing-remitting multiple sclerosis; SCQ = Self-administered Comorbidity Questionnaire; SPMS = Secondary progressive multiple sclerosis.
[a] Adjusted models adjusted for age, P-MSSS, FSS, and use of prescription antidepressant medication.
[b] Immunomodulatory medications queried include interferon-β-based medication, glatiramer acetate, alemtuzumab, cladribine, daclizumab, dimethyl fumarate, fingolimod, laquinimod, rituximab, teriflunomide, and natalizumab.

to become depressed, becoming stronger on adjustment. Baseline employment was associated with significantly lower risk of becoming depressed; however, on adjustment, these associations were abrogated. Participants who completed postgraduate education were significantly more likely to recover from depression between reviews, persisting on adjustment, whereas there was a reciprocal protective association of greater education against becoming depressed. While higher PRSES was not associated with change in depression state, those of lower PRSES had a significantly higher frequency of becoming depressed, persisting on adjustment.

Baseline overweight/obese BMI was associated with a significantly greater risk of becoming depressed at follow-up, though attenuating on adjustment (Table 6). Greater comorbidity number was associated with a significantly greater risk of becoming depressed ($p_{trend} < 0.001$), though this association became less dose-dependent and nonsignificant on adjustment. Baseline antidepressant use was associated with a 2.2-fold increased risk of becoming depressed, attenuating slightly on adjustment. Similar associations were seen for anxiolytic medication, but these were largely abrogated on adjustment for antidepressant use.

After adjustment, PRMS cases were 1.6-times more likely to lose depression, compared to benign/RRMS cases, while SPMS cases were over 2-fold more likely to gain depression. While relapse number was not associated with change in depression-state, a greater level of disability was associated with a significantly greater risk of becoming depressed, though this association was largely abrogated on adjustment for fatigue. Fatigue, on the other hand, was associated with 3-fold

**Table 3**
Associations of demographic covariates with positive depression-screen & grade vs normal at 2.5-year follow-up, as measured by PHQ-9.

| | *N* with PHQ-9 = 0–4 (Normal)(%) | *N* with PHQ-9 = 5–9 (Minimal)(%) | *N* with PHQ-9 = 10–14 (Major, mild)(%) | *N* with PHQ-9 = ≥15 (Major, moderate/ severe) (%) | aPR depression symptoms vs Normal | aPR Minimal depression symptoms vs Normal | aPR Major depression, mild vs Normal | aPR Major depression, moderate/severe vs Normal |
|---|---|---|---|---|---|---|---|---|
| Age | | | | | | | | |
| 18–38 | 121 (53.5%) | 58 (25.7%) | 23 (10.2%) | 24 (10.6%) | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] |
| >38–46 | 153 (49.4%) | 93 (30.0%) | 38 (12.3%) | 26 (8.4%) | 0.82 (0.61, 1.12) | 1.00 (0.78, 1.29) | 0.92 (0.59, 1.43) | 0.86 (0.57, 1.29) |
| >46–54 | 142 (42.8%) | 109 (32.8%) | 38 (11.5%) | 43 (13.0%) | 0.78 (0.58, 1.05) | 1.06 (0.84, 1.35) | 0.82 (0.52, 1.29) | 0.98 (0.68, 1.42) |
| >54–87 | 191 (48.2%) | 123 (31.1%) | 45 (11.4%) | 37 (9.3%) | **0.65 (0.48, 0.88)** | 0.97 (0.76, 1.23) | **0.64 (0.41, 1.00)** | 0.72 (0.48, 1.07) |
| *Trend:* | | | | | ***p* = 0.005** | *p = 0.82* | ***p* = 0.032** | *p = 0.13* |
| Marital status | | | | | | | | |
| Not married/partnered[a] | 125 (42.7%) | 88 (30.0%) | 39 (13.3%) | 41 (14.0%) | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] |
| Married/partnered | 478 (49.8%) | 292 (30.4%) | 104 (10.8%) | 86 (9.0%) | **0.79 (0.64, 0.98)** | 0.92 (0.77, 1.09) | 0.87 (0.65, 1.18) | **0.73 (0.55, 0.97)** |
| | | | | | ***p* = 0.033** | *p = 0.33* | *p = 0.37* | ***p* = 0.029** |
| Number of people in support network | | | | | | | | |
| 0 | 14 (35.0%) | 8 (20.0%) | 6 (15.0%) | 12 (30.0%) | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] |
| 1 | 108 (41.5%) | 71 (27.3%) | 45 (17.3%) | 36 (13.9%) | 0.82 (0.57, 1.18) | 1.17 (0.66, 2.06) | 0.99 (0.47, 2.09) | 0.97 (0.66, 1.42) |
| 2–5 | 374 (49.3%) | 243 (32.1%) | 81 (10.7%) | 60 (7.9%) | **0.50 (0.36, 0.72)** | 1.14 (0.65, 1.99) | 0.57 (0.27, 1.19) | **0.59 (0.40, 0.86)** |
| >5 | 87 (57.6%) | 46 (30.5%) | 9 (6.0%) | 9 (6.0%) | **0.38 (0.22, 0.64)** | 1.18 (0.66, 2.12) | 0.42 (0.16, 1.09) | 0.65 (0.36, 1.17) |
| *Trend:* | | | | | ***p* < 0.001** | *p = 0.71* | ***p* < 0.001** | ***p* = 0.001** |
| Employment status | | | | | | | | |
| Not employed | 211 (37.2%) | 194 (34.2%) | 83 (14.6%) | 80 (14.1%) | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] |
| Employed | 394 (57.3%) | 183 (26.6%) | 61 (8.9%) | 50 (7.3%) | **0.78 (0.64, 0.98)** | **0.79 (0.68, 0.92)** | **0.59 (0.42, 0.83)** | **0.73 (0.55, 0.99)** |
| | | | | | ***p* = 0.036** | ***p* = 0.003** | ***p* = 0.002** | ***p* = 0.044** |
| Level of education completed | | | | | | | | |
| None/primary/ | 93 (37.4%) | 80 (32.1%) | 32 (12.9%) | 44 (17.7%) | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] |
| secondary | 74 (38.7%) | 68 (35.6%) | 23 (12.0%) | 26 (13.6%) | 0.88 (0.66, 1.18) | 0.98 (0.79, 1.23) | 0.91 (0.58, 1.45) | 0.86 (0.60, 1.23) |
| Vocational school | 250 (53.0%) | 130 (27.5%) | 56 (11.9%) | 36 (7.6%) | 0.80 (0.62, 1.03) | 0.86 (0.71, 1.05) | 0.90 (0.63, 1.29) | 0.73 (0.52, 1.03) |
| Bachelor's degree | 190 (54.8%) | 102 (29.4%) | 32 (9.2%) | 23 (6.6%) | **0.67 (0.50, 0.89)** | 0.88 (0.71, 1.09) | 0.70 (0.46, 1.07) | **0.59 (0.40, 0.87)** |
| Post-graduate | | | | | ***p* = 0.004** | *p = 0.11* | *p = 0.072* | ***p* = 0.005** |
| study | | | | | | | | |
| *Trend:* | | | | | | | | |
| Perceived socioeconomic status relative to peers | | | | | | | | |
| Lower | 66 (26.7%) | 80 (32.4%) | 43 (17.4%) | 58 (23.5%) | **1.50 (1.18, 1.90)** | 1.00 (0.83, 1.20) | **1.49 (1.05, 2.11)** | **1.37 (1.03, 1.83)** |
| Same | 166 (42.5%) | 142 (36.3%) | 44 (11.3%) | 39 (10.0%) | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] |
| Higher | 371 (59.9%) | 160 (25.9%) | 55 (8.9%) | 33 (5.3%) | 0.83 (0.64, 1.08) | **0.75 (0.64, 0.89)** | 0.81 (0.58, 1.14) | **0.65 (0.43, 0.96)** |
| *Trend:* | | | | | ***p* < 0.001** | ***p* = 0.001** | ***p* = 0.001** | ***p* < 0.001** |

Analyses by log-multinomial regression, estimating a prevalence ratio (PR) (95% CI). All models adjusted for age, P-MSSS, FSS, and use of prescription antidepressant medication.
Figures in boldface denote statistical significance ($p < 0.05$). Figures in italics are *p*-values.
Abbreviations: FSS = Fatigue Severity Scale; PHQ = Patient Health Questionnaire; P-MSSS = Patient Determined Multiple Sclerosis Severity Score.
[a] Includes participants who were separated, divorced or widowed.

**Table 4**
Associations of clinical covariates with positive depression-screen & grade vs normal at 2.5-year follow-up, as measued by PHQ-9.

| | *N* with PHQ-9 = 0–4 (Normal) (%) | *N* with PHQ-9 = 5–9 (Minimal) (%) | *N* with PHQ-9 = 10–14 (Major, moderate/ severe) (%) | *N* with PHQ-9 = ≥15 (Major, moderate/ severe) (%) | aPR depression symptoms vs Normal | aPR Minimal depression symptoms vs Normal | aPR Major depression, mild vs Normal | aPR Major depression, moderate/severe vs Normal |
|---|---|---|---|---|---|---|---|---|
| BMI | | | | | | | | |
| Underweight/normal | 428 (55.9%) | 221 (28.9%) | 68 (8.9%) | 49 (6.4%) | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] |
| Overweight/obese | 177 (35.7%) | 162 (32.7%) | 76 (15.3%) | 81 (16.3%) | **1.56 (1.27, 1.92)** | **1.21 (1.05, 1.40)** | **1.61 (1.23, 2.10)** | **1.65 (1.22, 2.22)** |
| | | | | | ***p* < 0.001** | ***p* = 0.010** | ***p* = 0.001** | ***p* = 0.001** |
| Number of comorbidities as defined by SCQ | | | | | | | | |
| 0 | 380 (61.5%) | 170 (27.5%) | 38 (6.2%) | 30 (4.9%) | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] |
| 1 | 157 (45.6%) | 108 (31.4%) | 51 (14.8%) | 28 (8.1%) | **1.74 (1.30, 2.34)** | 1.17 (0.98, 1.39) | **2.06 (1.41, 2.99)** | **1.72 (1.09, 2.71)** |
| 2 | 50 (28.7%) | 67 (38.5%) | 25 (14.4%) | 32 (18.4%) | **2.11 (1.53, 2.90)** | **1.49 (1.22, 1.83)** | **2.33 (1.51, 3.58)** | **2.82 (1.83, 4.34)** |
| ≥3 | 20 (15.6%) | 38 (29.7%) | 30 (23.4%) | 40 (31.3%) | **3.09 (2.28, 4.19)** | **1.58 (1.26, 1.97)** | **3.56 (2.40, 5.29)** | **3.73 (2.46, 5.67)** |
| *Trend:* | | | | | ***p* < 0.001** | ***p* < 0.001** | ***p* < 0.001** | ***p* < 0.001** |
| Taking prescription antidepressant medication? | | | | | | | | |
| No | 558 (54.1%) | 306 (29.7%) | 94 (9.1%) | 73 (7.1%) | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] |
| Yes | 49 (21.0%) | 77 (33.1%) | 50 (21.5%) | 57 (24.5%) | **2.21 (1.81, 2.69)** | **1.36 (1.16, 1.59)** | **2.51 (1.91, 3.30)** | **2.57 (2.00, 3.32)** |
| | | | | | ***p* < 0.001** | ***p* < 0.001** | ***p* < 0.001** | ***p* < 0.001** |
| Taking prescription anxiolytic medication? | | | | | | | | |
| No | 585 (50.6%) | 346 (29.9%) | 120 (10.4%) | 106 (9.2%) | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] |
| Yes | 22 (20.6%) | 37 (34.6%) | 24 (22.4%) | 24 (22.4%) | **1.32 (1.03, 1.69)** | **1.38 (1.12, 1.70)** | **1.59 (1.16, 2.16)** | **1.49 (1.13, 1.96)** |
| | | | | | ***p* = 0.030** | ***p* = 0.003** | ***p* = 0.004** | ***p* = 0.005** |
| Type of MS at completion of survey | | | | | | | | |
| Benign/RRMS | 432 (52.3%) | 237 (28.7%) | 87 (10.5%) | 70 (8.5%) | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] |
| PPMS | 65 (35.0%) | 76 (04.9%) | 19 (10.2%) | 26 (14.0%) | 0.88 (0.64, 1.19) | 1.07 (0.88, 1.29) | 0.93 (0.58, 1.48) | 1.07 (0.75, 1.53) |
| SPMS | 43 (42.2%) | 27 (26.5%) | 19 (18.65) | 13 (12.8%) | 1.23 (0.86, 1.76) | 0.80 90.59, 1.11) | 1.20 (0.76, 1.90) | 0.86 (0.49, 1.53) |
| PRMS | 6 (27.3%) | 8 (36.4%) | 5 (22.7%) | 3 (13.6%) | 1.16 (0.64, 2.08) | 1.13 (0.77, 1.66) | 1.74 (1.05, 2.90) | 1.70 (0.89, 3.24) |
| Unsure/other | 61 (48.8%) | 33 (26.4%) | 14 (11.2%) | 17 (13.6%) | 1.15 (0.83, 1.60) | 0.86 (0.64, 1.14) | 1.11 (0.68, 1.81) | 0.99 (0.66, 1.48) |
| Number of doctor-diagnosed relapses in preceding 12 months | | | | | | | | |
| 0 | 501 (52.2%) | 280 (29.2%) | 96 (10.0%) | 83 (8.7%) | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] |
| 1 | 75 (37.0%) | 68 (33.5%) | 33 (16.3%) | 27 (13.3%) | 1.20 (0.94, 1.53) | 1.09 (0.91, 1.31) | 1.35 (0.99, 1.85) | 1.09 (0.76 ,1.54) |
| 2 | 9 (22.5%) | 18 (45.0%) | 65 (15.0%) | 7 (17.5%) | 1.13 (0.73, 1.75) | **1.48 (1.12, 1.97)** | 1.91 (0.94, 3.88) | 1.12 (0.79, 1.60) |
| ≥3 | 6 (27.3%) | 3 (13.6%) | 5 (22.7%) | 8 (36.4%) | **1.61 (1.08, 2.39)** | 0.62 (0.25, 1.53) | 1.18 (0.54, 2.59) | 1.07 (0.65, 1.76) |
| *Trend:* | | | | | ***p* = 0.023** | *p = 0.26* | *p = 0.091* | *p = 0.51* |
| P-MSSS disability | | | | | | | | |
| Mild disability (0–3) | 237 (61.6%) | 102 (26.5%) | 31 (8.1%) | 15 (3.9%) | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] |
| Moderate disability | 193 (51.1%) | 112 (29.6%) | 33 (8.7%) | 40 (10.6%) | 1.12 (0.81, 1.54) | 0.97 (0.79, 1.19) | 0.95 (0.62, 1.44) | 1.40 (0.83, 2.36) |
| (4–6) | 173 (35.5%) | 167 (34.3%) | 76 (15.6%) | 71 (14.6%) | **1.54 (1.15, 2.08)** | 1.11 (0.91, 1.34) | **1.64 (1.14, 2.36)** | **1.73 (1.04, 2.87)** |
| Severe disability | | | | | ***p* = 0.001** | *p = 0.25* | ***p* = 0.004** | ***p* = 0.016** |
| (>6) | | | | | | | | |
| *Trend:* | | | | | | | | |
| Fatigue, as defined by FSS > 35 | | | | | | | | |
| No fatigue | 371 (80.0%) | 65 (14.0%) | 25 (5.4%) | 3 (0.7%) | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] |
| Fatigue | 210 (27.7%) | 305 (40.3%) | 118 (15.6%) | 124 (16.4%) | **4.20 (2.83, 6.24)** | **3.79 (2.97, 4.85)** | **4.51 (2.92, 6.96)** | **31.73 (9.80, 102.69)** |
| | | | | | ***p* < 0.001** | ***p* < 0.001** | ***p* < 0.001** | ***p* < 0.001** |
| Disease duration from symptom onset, years | | | | | | | | |
| 2.91 – 8.19 | 194 (61.0%) | 74 (23.3%) | 32 (10.1%) | 18 (5.7%) | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] |
| >8.19 – 14.23 | 153 (49.0%) | 93 (29.8%) | 31 (9.9%) | 35 (11.2%) | 1.23 (0.90, 1.67) | 1.16 (0.92, 1.46) | 1.10 (0.73, 1.66) | **1.79 (1.14, 2.82)** |
| >14.23 – 23.20 | 150 (47.0%) | 94 (29.5%) | 42 (13.2%) | 33 (10.3%) | 1.29 (0.93, 1.78) | 1.06 (0.83, 1.36) | 1.27 (0.85, 1.90) | **1.67 (1.03, 2.71)** |
| >23.20 – 56.14 | 109 (34.9%) | 122 (39.1%) | 38 (12.2%) | 43 (13.8%) | 1.30 (0.92, 1.84) | **1.37 (1.08, 1.74)** | 1.48 (0.95, 2.31) | **2.16 (1.31, 3.56)** |
| *Trend:* | | | | | *p = 0.16* | ***p* = 0.017** | *p = 0.059* | ***p* = 0.005** |

(*continued on next page*)

**Table 4** (*continued*)

| | *N* with PHQ-9 = 0–4 (Normal) (%) | *N* with PHQ-9 = 5–9 (Minimal) (%) | *N* with PHQ-9 = 10–14 (Major, moderate/ severe) (%) | *N* with PHQ-9 = ≥ 15 (Major, moderate/ severe) (%) | aPR depression symptoms vs Normal | aPR Minimal depression symptoms vs Normal | aPR Major depression, mild vs Normal | aPR Major depression, moderate/severe vs Normal |
|---|---|---|---|---|---|---|---|---|
| Taking any of the 11 specified immunomodulatory medications?[a] | | | | | | | | |
| None | 357 (51.2%) | 203 (29.1%) | 74 (10.6%) | 64 (9.2% | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] |
| Interferon-β | 50 (42.0%) | 33 (27.7%) | 13 (10.9%) | 23 (19.3%) | **1.34 (1.03, 1.75)** | 1.16 (0.88, 1.51) | 1.11 (0.71, 1.75) | **1.39 (1.00, 1.94)** |
| Other | 200 (44.7%) | 147 (32.9%) | 57 (12.8%) | 43 (9.6%) | 0.91 (0.73, 1.14) | 1.07 (0.92, 1.24) | 0.99 (0.74, 1.32) | 0.94 (0.69, 1.30) |

Analyses by log-multinomial regression, estimating a prevalence ratio (PR) (95% CI). All models adjusted for age, P-MSSS, FSS, and use of prescription antidepressant medication.
Figures in boldface denote statistical significance ($p < 0.05$). Figures in italics are p-values.
Abbreviations: BMI = Body mass index; FSS = Fatigue Severity Scale; PHQ = Patient Health Questionnaire; P-MSSS = Patient Determined Multiple Sclerosis Severity Score; PPMS = Primary progressive multiple sclerosis; PRMS = Progressive-relapsing multiple sclerosis; RRMS = Relapsing-remitting multiple sclerosis; SCQ = Self-administered Comorbidity Questionnaire; SPMS = Secondary progressive multiple sclerosis.
[a] Immunomodulatory medications queried include interferon-β-based medication, glatiramer acetate, alemtuzumab, cladribine, daclizumab, dimethyl fumarate, fingolimod, laquinimod, rituximab, teriflunomide, and natalizumab.

greater risk of becoming depressed, largely robust to adjustment for disability. No consistent or material associations were seen between immunomodulatory medication use and subsequent change in depression-state.

## 5. Discussion

We found PHQ-2 positive depression-screen prevalence fell significantly during follow-up, from 19.1% to 14.5%, though this may be an underestimate since the more comprehensive PHQ-9 found an estimated depression-screen prevalence of 21.7%. These results are in keeping with the literature, a systematic review finding an MS PHQ-9 depression-screen prevalence of 23.9% in MS patients (Boeschoten et al., 2017). We replicated our previous findings (Taylor et al., 2014), showing that BMI, comorbidity number, fatigue, and disability were significantly predictive of positive depression-screen, while marital status, employment, and education were negatively associated with risk of depression-screen. Also, many of these factors were significantly predictive of change in depression state.

Depression is a common comorbidity in MS, affecting between one-quarter to one-third of patients (Boeschoten et al., 2017). The mechanisms underlying depression in MS are uncertain, though unlike in the general population, where depression is largely of genetic aetiology, in MS it may reflect common pathological processes (Sadovnick et al., 1996). Given the interrelationship of the immune and nervous systems at the hypothalamus-pituitary-adrenal axis, depression symptoms may be due to the same inflammatory processes driving MS symptoms (Solaro et al., 2018). By identifying the determinants of depression in MS, we might predict and potentially reduce depression among people with MS.

Progressive MS type, relapse number, disability and fatigue were all associated with increased risk of positive depression-screen, though of these, only fatigue persisted on adjustment. These results suggest that fatigue, not disability, is the driver of depression. Disability and fatigue's strong associations with depression have been demonstrated both in early and established MS (Berzins et al., 2017; Brown et al., 2009; Koch et al., 2009; Simpson et al., 2016; Wood et al., 2012). Greeke and colleagues found that persons with significant fatigue were at especial risk of developing depression (Greeke et al., 2017), while Gunzler and colleagues found that baseline disability strongly predicted depression trajectory among 3507 MS patients (Gunzler et al., 2016). Moreover, there is some indication that treating depression may impact perceived fatigue (Mohr et al., 2003), potentially facilitating a feedback cycle to improve mental quality of life.

Overweight/obese BMI was significantly associated with increased risk of newly positive depression-screen; however, these associations became non-significant on adjustment. This suggests that despite known inflammatory effects of adiposity (Capuron et al., 2017), its impact on depression was not independent of clinical factors. Comorbidity number showed a dose-dependent association with increased risk of newly positive depression-screen. Comorbidities have been associated with clinical outcomes in MS (Marrie and Horwitz, 2010), and while some are potentially due to common inflammatory antecedents (Rossi et al., 2017), others like depression could be attributable both to common pathophysiological processes, and to MS symptoms and other comorbidities. Thus, it is not surprising that comorbidity number was positively associated with depression, even after adjustment for disability and fatigue. The positive associations seen for antidepressant and anxiolytic medication and depression-screen are most likely reverse causal in nature, whereby those with depression are more likely to be taking these medications, rather than a deleterious effect of the medications on mood.

Beyond clinical features, marital status, employment, socio-economic status, and education were associated with depression state. Being employed or partnered predicted a significantly reduced risk of newly positive depression-screen. However, while marital status's

**Table 5**
Demographic predictors of change in PHQ-2 depression state between baseline and 2.5-year follow-up.

| | *N* with positive depression-screen at both baseline & follow-up (row %) | *N* with positive depression-screen at baseline, not at follow-up (row %) | RR loss of positive depression-screen vs positive depression-screen at both timepoints | aRR[a] loss of positive depression-screen vs positive depression-screen at both timepoints | *N* with negative depression-screen at both baseline & follow-up (row %) | *N* with negative depression-screen at baseline but with positive depression-screen at follow-up (row %) | RR gain of positive depression-screen vs negative depression-screen at both timepoints | aRR[a] gain of positive depression-screen vs negative depression-screen at both timepoints |
|---|---|---|---|---|---|---|---|---|
| 18 – 38 | 9 (29.0%) | 22 (71.0%) | 1.00 [Reference] | 1.00 [Reference] | 170 (90.4%) | 18 (9.6%) | 1.00 [Reference] | 1.00 [Reference] |
| >38 – 46 | 16 (44.4%) | 20 (55.6%) | 0.75 (0.52, 1.08) | 0.83 (0.58, 1.19) | 243 (90.3%) | 26 (9.7%) | 0.97 (0.55, 1.71) | 1.16 (0.70, 1.91) |
| >46 – 54 | 25 (53.2%) | 22 (46.8%) | **0.66 (0.45, 0.96)** | 0.76 (0.53, 1.08) | 245 (90.1%) | 27 (9.9%) | 1.11 (0.64, 1.94) | 0.85 (0.50, 1.45) |
| >54 – 87 | 21 (40.4%) | 31 (59.6%) | 0.81 (0.59, 1.11) | 0.85 (0.59, 1.21) | 317 (90.8%) | 32 (9.2%) | 1.05 (0.61, 1.80) | 0.81 (0.46, 1.44) |
| *Trend:* | | | *p = 0.25* | *p = 0.26* | | | *p = 0.75* | *p = 0.25* |
| Married/partnered at baseline? | | | | | | | | |
| No | 24 (45.3%) | 29 (54.7%) | 1.00 [Reference] | 1.00 [Reference] | 200 (87.7%) | 28 (12.3%) | 1.00 [Reference] | 1.00 [Reference] |
| Yes | 45 (40.5%) | 66 (59.5%) | 1.09 (0.82, 1.45) | 1.10 (0.82, 1.47) | 766 (91.4%) | 72 (8.6%) | 0.74 (0.49, 1.11) | **0.62 (0.41, 0.94)** |
| | | | *p = 0.57* | *p = 0.55* | | | *p = 0.14* | ***p = 0.024*** |
| Number of people in support network at baseline | | | | | | | | |
| 0 | 6 (60.0%) | 4 (40.0%) | 1.00 [Reference] | 1.00 [Reference] | 33 (84.6%) | 6 (15.4%) | 1.00 [Reference] | 1.00 [Reference] |
| 1 | 20 (40.0%) | 30 (60.0%) | 1.44 (0.64, 3.27) | 1.65 (0.62, 4.37) | 178 (90.4%) | 19 (9.6%) | 0.67 (0.29, 1.55) | 0.54 (0.25, 1.19) |
| 2 – 5 | 35 (39.3%) | 54 (60.7%) | 1.43 (0.64, 3.20) | 1.68 (0.64, 4.38) | 607 (90.3%) | 65 (9.7%) | 0.68 (0.32, 1.44) | **0.45 (0.23, 0.89)** |
| >5 | 10 (62.5%) | 6 (37.5%) | 0.86 (0.32, 2.34) | 1.14 (0.37, 3.46) | 151 (93.2%) | 11 (6.8%) | 0.55 (0.22, 1.38) | **0.42 (0.18, 0.95)** |
| *Trend:* | | | *p = 0.61* | *p = 0.96* | | | *p = 0.33* | *p = 0.11* |
| Employment status at baseline | | | | | | | | |
| Not employed | 33 (38.4%) | 53 (61.6%) | 1.00 [Reference] | 1.00 [Reference] | 380 (88.0%) | 52 (12.0%) | 1.00 [Reference] | 1.00 [Reference] |
| Employed | 37 (46.8%) | 42 (53.2%) | 0.87 (0.67, 1.13) | 0.87 (0.65, 1.16) | 594 (92.1%) | 51 (7.9%) | **0.69 (0.48, 0.99)** | 0.93 (0.62, 1.38) |
| | | | *p = 0.30* | *p = 0.33* | | | ***p = 0.045*** | *p = 0.71* |
| Level of education completed | | | | | | | | |
| None/primary/ | 21 (50.0%) | 21 (50.0%) | 1.00 [Reference] | 1.00 [Reference] | 168 (87.1%) | 25 (13.0%) | 1.00 [Reference] | 1.00 [Reference] |
| secondary | 15 (44.1%) | 19 (55.9%) | 1.06 (0.69, 1.62) | 1.27 (0.81, 1.98) | 135 (88.2%) | 18 (11.8%) | 0.92 (0.52, 1.63) | 1.13 (0.63, 2.03) |
| Vocational | 30 (49.2%) | 31 (50.8%) | 0.99 (0.68, 1.46) | 1.04 (0.70, 1.56) | 379 (91.6%) | 35 (8.5%) | 0.66 (0.41, 1.07) | 0.79 (0.49, 1.28) |
| school | 5 (17.9%) | 23 (82.1%) | **1.58 (1.12, 2.23)** | **1.74 (1.20, 2.53)** | 290 (92.4%) | 24 (7.6%) | **0.57 (0.34, 0.97)** | 0.70 (0.40, 1.22) |
| Bachelor's | | | *p = 0.057* | *p = 0.074* | | | ***p = 0.018*** | *p = 0.11* |
| degree | | | | | | | | |
| Post- | | | | | | | | |
| graduate study | | | | | | | | |
| *Trend:* | | | | | | | | |
| Perceived socioeconomic status relative to peers | | | | | | | | |
| Lower | 26 (44.8%) | 32 (55.2%) | 1.00 (0.73, 1.38) | 0.99 (0.72, 1.38) | 141 (80.6%) | 34 (19.4%) | **1.87 (1.20, 2.90)** | **1.61 (1.02, 2.53)** |
| Same | 27 (43.6%) | 35 (56.5%) | 1.00 [Reference] | 1.00 [Reference] | 300 (90.4%) | 32 (9.6%) | 1.00 [Reference] | 1.00 [Reference] |
| Higher | 18 (39.1%) | 28 (60.9%) | 1.08 (0.79, 1.48) | 1.06 (0.76, 1.48) | 527 (93.4%) | 37 (6.6%) | 0.72 (0.46, 1.13) | 0.78 (0.49, 1.24) |
| *Trend:* | | | *p = 0.65* | *p = 0.67* | | | ***p < 0.001*** | ***p = 0.005*** |

Analyses by log-binomial regression, estimating a risk ratio (RR) (95% CI).
Figures in boldface denote statistical significance ($p < 0.05$). Figures in italics are p-values.
Abbreviations: FSS = Fatigue Severity Scale; PHQ = Patient Health Questionnaire; P-MSSS = Patient Determined Multiple Sclerosis Severity Score.
[a] Adjusted models adjusted for age, baseline P-MSSS, baseline FSS, baseline use of antidepressant, and baseline PHQ-2 score.

association persisted on adjustment, that of employment was eliminated. Notably, while a higher PRSES was not significantly associated with change in depression, lower PRSES was robustly associated with significantly greater risk of becoming depressed. Given the subjective nature of PRSES and given that employment was not independently associated with change in depression, it is potentially more the perception rather than status itself which affected depression. The impacts of demographic characteristics on depression have been shown previously. In a study of 451 US veterans, Williams and colleagues found unemployment, lower income and lack of partner were positively associated with depression (Williams et al., 2005). Likewise, a cohort study of 236 patients followed for five years in early MS found that depression was significantly more common among unemployed participants (Simpson et al., 2016). Given the potential for positive feedback, whereby unemployment leads to greater depression (Maier et al., 2016), this could exacerbate symptoms, leading to worse quality of life.

### 5.1. Strengths and limitations

A major strength of our sample was the breadth of data on lifestyle and clinical factors. Our data are self-reported so the potential for recall bias exists. We recruited and retained a large sample size, including people with all types of MS from geographically diverse backgrounds. Validated tools were used wherever possible and potential confounders were adjusted for. Not all participants responded to every question and thus, there was some missing data. Accordingly, all multivariate models were complete-case analysis, restricted to those with data on all model parameters. Reverse causality cannot be excluded from some associations. However, the biological plausibility, dose-dependency and consistency with existing literature support the veracity of these findings.

Potentially, severely depressed people might not participate in this study and thus, our assessment of the frequency and determinants of severe depression could be affected. Our sample may be biased due to participants being recruited via online platforms, potentially recruiting a healthier cohort. In addition, there was appreciable attrition between baseline and follow-up reviews, with a retention rate of 56.8%. While there was some evidence that those retained in the study engaged in less unhealthy behaviours like smoking, other behaviours like alcohol, physical activity and supplement use were not materially different, and clinical characteristics like disability or fatigue were comparable. However, significantly more people with depression risk at baseline were lost to follow-up, suggesting that our estimates of depression prevalence at follow-up may underestimate the true prevalence, and that associations with depression state may also be affected. This may also account for the drop in depression during follow-up.

Our lack of data on the PHQ-9 at baseline does preclude the assessment of change in this parameter. While we can calculate PHQ-2 at both timepoints and thus assess change in this, the absence of data on the more comprehensive PHQ-9 at baseline is a limitation.

**Table 6**
Clinical predictors of change in PHQ-2 depression state between baseline and 2.5-year follow-up.

| | *N* with positive depression-screen at both baseline & follow-up (row %) | *N* with positive depression-screen at baseline, not at follow-up (row %) | RR loss of positive depression-screen vs positive depression-screen at both timepoints | aRR[a] loss of positive depression-screen vs positive depression-screen at both timepoints | *N* with negative depression-screen at both baseline & follow-up (row %) | *N* with negative depression-screen at baseline but with positive depression-screen at follow-up (row %) | RR gain of positive depression-screen vs negative depression-screen at both timepoints | aRR[a] gain of positive depression-screen vs negative depression-screen at both timepoints |
|---|---|---|---|---|---|---|---|---|
| Overweight/obese BMI at baseline | | | | | | | | |
| No | 32 (42.1%) | 44 (57.9%) | 1.00 [Reference] | 1.00 [Reference] | 651 (92.3%) | 54 (7.7%) | 1.00 [Reference] | 1.00 [Reference] |
| Yes | 39 (43.3%) | 51 (56.7%) | 0.98 (0.76, 1.28) | 1.00 (0.76, 1.33) | 322 (86.8%) | 49 (13.2%) | **1.65 (1.15, 2.36)** | 1.42 (0.98, 2.06) |
| | | | *p = 0.91* | *p = 0.99* | | | ***p = 0.007*** | *p = 0.061* |
| Number of comorbidities as defined by SCQ at baseline | | | | | | | | |
| 0 | 9 (42.9%) | 12 (57.1%) | 1.00 [Reference] | 1.00 [Reference] | 406 (94.4%) | 24 (5.6%) | 1.00 [Reference] | 1.00 [Reference] |
| 1 | 12 (30.8%) | 27 (69.2%) | 1.27 (0.83, 1.94) | 1.34 (0.89, 2.04) | 295 (91.6%) | 27 (8.4%) | 1.42 (0.84, 2.40) | 1.23 (0.71, 2.13) |
| 2 | 18 (41.9%) | 25 (58.1%) | 1.07 (0.68, 1.68) | 1.05 (0.65, 1.68) | 169 (84.1%) | 32 (15.9%) | **2.31 (1.38, 3.87)** | **1.77 (1.03, 3.04)** |
| ≥3 | 32 (50.8%) | 31 (49.2%) | 0.94 (0.60, 1.49) | 1.00 (0.62, 1.60) | 105 (84.0%) | 20 (16.0%) | **2.29 (1.32, 3.99)** | 1.47 (0.77, 2.82) |
| *Trend:* | | | *p = 0.32* | *p = 0.38* | | | ***p < 0.001*** | *p = 0.11* |
| Taking prescription antidepressant medication at baseline? | | | | | | | | |
| No | 44 (42.3%) | 60 (57.7%) | 1.00 [Reference] | 1.00 [Reference] | 853 (92.2%) | 72 (7.8%) | 1.00 [Reference] | 1.00 [Reference] |
| Yes | 27 (43.6%) | 35 (56.5%) | 1.01 (0.77, 1.32) | 0.93 (0.70, 1.25) | 122 (79.7%) | 31 (20.3%) | **2.21 (1.50, 3.28)** | **2.00 (1.35, 2.96)** |
| | | | *p = 0.97* | *p = 0.64* | | | ***p < 0.001*** | ***p = 0.001*** |
| Taking prescription anxiolytic medication at baseline? | | | | | | | | |
| No | 60 (42.3%) | 82 (57.8%) | 1.00 [Reference] | 1.00 [Reference] | 912 (91.5%) | 85 (8.5%) | 1.00 [Reference] | 1.00 [Reference] |
| Yes | 11 (45.8%) | 13 (54.2%) | 0.96 (0.64, 1.44) | 0.86 (0.52, 1.40) | 63 (77.8%) | 18 (22.2%) | **2.21 (1.43, 3.42)** | 1.52 (0.90, 2.58) |
| | | | *p = 0.84* | *p = 0.54* | | | ***p < 0.001*** | *p = 0.12* |
| Type of MS at completion of survey | | | | | | | | |
| Benign/RRMS | 41 (40.6%) | 60 (59.4%) | 1.00 [Refeence] | 1.00 [Reference] | 660 (92.8%) | 51 (7.2%) | 1.00 [Reference] | 1.00 [Reference] |
| PPMS | 19 (61.3%) | 12 (38.7%) | 0.65 (0.41, 1.04) | 0.61 (0.36, 1.05) | 135 (88.2%) | 18 (11.8%) | 1.44 (0.86, 2.41) | 1.05 (0.55, 1.99) |
| SPMS | 4 (25.0%) | 12 (75.0%) | 1.19 (0.85, 1.64) | 1.12 (0.76,1.66) | 66 (80.5%) | 16 (19.5%) | **2.55 (1.54, 4.22)** | **2.06 (1.10, 3.86)** |
| PRMS | 1 (16.7%) | 5 (83.3%) | 1.46 (0.97, 2.19) | **1.60 (1.00, 2.56)** | 13 (86.7%) | 2 (13.3%) | 1.93 (0.47, 7.88) | 1.39 (0.34, 5.67) |
| Unsure/ other | 6 (50.0%) | 6 (50.0%) | 0.92 (0.52, 1.62) | 0.92 (0.52, 1.63) | 97 (85.8%) | 16 (14.2%) | **1.83 (1.09, 3.06)** | 1.56 (0.86, 2.83) |
| Number of doctor-diagnosed relapses in preceding 12 months | | | | | | | | |
| 0 | 45 (41.7%) | 63 (58.3%) | 1.00 [Reference] | 1.00 [Reference] | 754 (91.0%) | 75 (9.1%) | 1.00 [Reference] | 1.00 [Reference] |
| 1 | 17 (47.2%) | 19 (52.8%) | 0.90 (0.64, 1.27) | 0.88 (0.61, 1.27) | 148 (89.2%) | 18 (10.8%) | 1.15 (0.71, 1.88) | 1.09 (0.65, 1.82) |
| 2 | 3 (33.3%) | 6 (66.7%) | 1.23 (0.76, 2.00) | 1.36 (0.87, 2.12) | 28 (90.3%) | 3 (9.7%) | 0.96 (0.32, 2.83) | 0.82 (0.26, 2.63) |
| ≥3 | 3 (50.0%) | 3 (50.0%) | 0.85 (0.37, 1.96) | 0.87 (0.39, 1.97) | 12 (70.6%) | 5 (29.4%) | **2.93 (1.38, 6.21)** | 2.09 (0.85, 5.12) |
| *Trend:* | | | *p = 0.86* | *p = 0.95* | | | *p = 0.074* | *p = 0.39* |
| P-MSSS disability at baseline | | | | | | | | |
| Mild disability (0–3) | 12 (38.7%) | 19 (61.3%) | 1.00 [Reference] | 1.00 [Reference] | 370 (93.9%) | 24 (6.1%) | 1.00 [Reference] | 1.00 [Reference] |
| | 23 (46.9%) | 26 (53.1%) | 0.82 (0.57, 1.27) | 0.88 (0.57, 1.34) | 283 (93.4%) | 20 (6.6%) | 1.04 (0.59, 1.83) | 0.76 (0.42, 1.37) |
| Moderate disability (4–6) | 35 (41.2%) | 50 (58.8%) | 0.97 (0.69, 1.37) | 1.02 (0.70, 1.48) | 313 (84.6%) | 57 (15.4%) | **2.14 (1.36, 3.37)** | 1.41 (0.86, 2.32) |
| | | | *p = 0.93* | *p = 0.69* | | | ***p = 0.001*** | *p = 0.11* |
| Severe disability (>6) | | | | | | | | |
| *Trend:* | | | | | | | | |
| Fatigue, as defined by FSS>35 at baseline | | | | | | | | |
| No fatigue | 5 (38.5%) | 8 (61.5%) | 1.00 [Reference] | 1.00 [Reference] | 423 (96.6%) | 15 (3.4%) | 1.00 [Reference] | 1.00 [Reference] |
| Fatigue | 62 (43.1%) | 82 (56.9%) | 0.90 (0.58, 1.42) | 0.82 (0.52, 1.30) | 513 (86.2%) | 82 (13.8%) | **3.28 (1.89, 5.72)** | **2.91 (1.59, 5.36)** |
| | | | *p = 0.66* | *p = 0.40* | | | ***p < 0.001*** | ***p = 0.001*** |
| Disease duration from symptom onset, years | | | | | | | | |
| 2.91 – 8.19 | 13 (41.9%) | 18 (58.1%) | 1.00 [Reference] | 1.00 [Reference] | 259 (92.8%) | 20 (7.2%) | 1.00 [Reference] | 1.00 [Reference] |
| >8.19 – 14.23 | 21 (48.8%) | 22 (51.2%) | 0.86 (0.57, 1.30) | 1.00 (0.67, 1.51) | 245 (91.8%) | 22 (8.2%) | 1.21 (0.68, 2.14) | 1.16 (0.64, 2.11) |
| | 14 (36.8%) | 24 (63.2%) | 1.06 (0.72, 1.55) | 1.23 (0.81, 1.88) | 239 (87.9%) | 33 (12.1%) | **1.78 (1.06, 3.00)** | 1.62 (0.92, 2.84) |
| >14.23 – 23.20 | 23 (42.6%) | 31 (57.4%) | 0.97 (0.66, 1.42) | 1.21 (0.76, 1.93) | 229 (89.1%) | 28 (10.9%) | 1.60 (0.93, 2.75) | 1.27 (0.68, 2.38) |
| | | | *p = 0.83* | *p = 0.43* | | | ***p = 0.031*** | *p = 0.30* |
| >23.20 – 56.14 | | | | | | | | |
| *Trend:* | | | | | | | | |
| Taking any of the 11 specified immunomodulatory medications at baseline?[b] | | | | | | | | |
| None | 31 (47.0%) | 35 (53.0%) | 1.00 [Reference] | 1.00 [Reference] | 525 (91.0%) | 52 (9.0%) | 1.00 [Reference] | 1.00 [Reference] |
| Interferon-β | 15 (33.3%) | 30 (66.7%) | 1.25 (0.92, 1.70) | 1.30 (0.59, 1.77) | 163 (89.6%) | 19 (10.4%) | 1.15 (0.70, 1.89) | 1.16 (0.68, 1.97) |
| Other | 25 (45.5%) | 30 (54.6%) | 1.03 (0.74, 1.43) | 1.05 (0.74, 1.49) | 287 (90.0%) | 32 (10.0%) | 1.11 (0.74, 1.67) | 1.15 (0.76, 1.75) |

Analyses by log-binomial regression, estimating a risk ratio (RR) (95% CI).
Figures in boldface denote statistical significance ($p < 0.05$). Figures in italics are *p*-values.
Abbreviations: BMI = Body mass index; FSS = Fatigue Severity Scale; PHQ = Patient Health Questionnaire; P-MSSS = Patient Determined Multiple Sclerosis Severity Score; PPMS = Primary progressive multiple sclerosis; PRMS = Progressive-relapsing multiple sclerosis; RRMS = Relapsing-remitting multiple sclerosis; SCQ = Self-administered Comorbidity Questionnaire; SPMS = Secondary progressive multiple sclerosis.
[a] Adjusted models adjusted for age, baseline P-MSSS, baseline FSS, baseline use of antidepressant, and baseline PHQ-2 score.
[b] Immunomodulatory medications queried include interferon-β-based medication, glatiramer acetate, alemtuzumab, cladribine, daclizumab, dimethyl fumarate, fingolimod, laquinimod, rituximab, teriflunomide, and natalizumab.

Another potential issue is the poor sensitivity – only 56.9% - of the PHQ-2 against the PHQ-9, which was considered the referent standard here given its greater comprehensiveness. The PHQ-2 and PHQ-9 had good sensitivity (87% and 95%, respectively) in comparison to clinically diagnosed depression (Kroenke et al., 2001; Lowe et al., 2005), but the PHQ-2 has not been compared to the PHQ-9 as we have done here. While both the PHQ-2 and PHQ-9 have fair sensitivity (84 and 80%, respectively) in comparison to a clinical diagnosis of major depressive disorder (Gilbody et al., 2007), each measure has some variability in its sensitivity in different patient populations. It may be that the PHQ-2 was less sensitive in our sample than it might be in other populations.

Since fatigue can be a symptom of depression and MS, another limitation is that our measure of depression by the PHQ-9 which includes a question about energy, could realise higher PHQ-9 scores in these individuals. It is encouraging, though, that we actually showed even stronger associations between fatigue and PHQ-2 depression, suggesting that while there is an element of fatigue in PHQ-9, the associations seen between fatigue and depression were not solely a function of this.

## 6. Conclusions

In a large prospective cohort study of depressive symptoms in MS patients, we found the frequency of positive depression-screen was roughly 14–21%, depending which measure was used, but showed a significant decline over 2.5-years follow-up. The principal factors associated with positive depression-screen and its change included marital status, employment, education, PRSES, BMI, disability, fatigue, and antidepressant use. While some of these factors are not modifiable, our results suggest that efforts to reduce fatigue in people with MS may have a significant positive effect on depression in this population.

### 6.1. Ethics approval and consent to participate

The Health Sciences Human Ethics Sub-Committee at the University of Melbourne provided ethical approval for the study (Ethics ID: 1545102). Participants were asked to read the participant information and to consent before entering the survey.

### 6.2. Availability of data and material

Data may not be shared due to the conditions approved by our institutional ethics committee, in that all data are stored as re-identifiable information at the University of Melbourne in the form of password-protected computer databases, and only the listed investigators have access to the data. All data have been reported on a group basis, summarising the group findings rather than individual findings so personal information cannot be identified. Therefore, we can supply aggregate group data on request. Readers may contact George Jelinek or Tracey Weiland.

## 7. Authors' contributions

GJ, TW, KT, SSJ, CB and AL are responsible for study concept; SSJ, CB and EOK contributed to cohort management and cleaned and prepared the data for analysis. SSJ undertook data analyses. SSJ drafted and edited the manuscript; TW, GJ and KT contributed to editing an earlier version of the manuscript. All authors approved the final version of the manuscript.

### 7.1. Competing interests

GJ receives royalties for his books, *Overcoming Multiple Sclerosis* and *Recovering from Multiple Sclerosis*. GJ, SN and KT have received remuneration for conducting lifestyle educational workshops for people with MS.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2019.02.014.

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